American Journal of Medical Genetics 68:466–471 (1997)

Pattern of Malformations in the Axial Skeleton in Human Trisomy 21 Fetuses

Jean W. Keeling,[1] Birgit Fischer Hansen,[2] and Inger Kjær[3*]

[1]*Department of Pathology and Cytogenetics, Royal Hospital for Sick Children, Edinburgh, Scotland*
[2]*Department of Pathology, Hvidovre University Hospital, Copenhagen, Denmark*
[3]*Department of Orthodontics, School of Dentistry, University of Copenhagen, Copenhagen, Denmark*

In the present study, we analyzed the development of the axial skeleton in human trisomy 21 fetuses and defined the fields in the axial skeleton affected in this form of aneuploidy. We investigated 31 human fetuses with trisomy 21, gestational ages 12–24 weeks, on the basis of radiographs of midsagittal tissue blocks of the axial skeleton, comprising the cranial base and the spine. Malformation or agenesis of the nasal bone was present in 19 of 31 fetuses. Nineteen cases had vertebral malformations. Fourteen fetuses had malformations in the cervical region, four in the thoracic and eight in the lumbosacral region. In 1 of 31 fetuses, malformation was seen in the basilar part of the occipital bone. The basisphenoid component appeared scallop-shaped in 30 cases.

The pattern of axial skeletal malformations in trisomy 21 fetuses recorded here has not been described previously. Comparison is made with our recent study of trisomy 18, where the pattern of axial skeletal malformations was quite different. It is recommended that axial skeletal radiography should be part of the autopsy of fetuses where chromosome abnormalities are known or suspected. Am. J. Med. Genet. 68:466–471, 1997.

KEY WORDS: development; skeleton; fetal; genetic radiography; trisomy 21

INTRODUCTION

In a previous investigation of the axial skeleton in trisomy 18 fetuses, it was shown that malformations occurred in the thoracic and/or lumbosacral fields in all fetuses. Malformations also always occurred in the occipital field of the axial part of the cranial base, whereas the field including the nasal bones was not always affected, and malformations were not found in the cervical field [Kjær et al., 1996]. The study of trisomy 18 fetuses showed, like earlier studies on anencephaly [Kjær et al., 1994a], that there are regional differences in the occurrence of malformations along the axial skeleton. Against this background, it seems appropriate to investigate the pattern of malformation in the axial skeleton in fetuses with various genetic disorders. The purpose of the present investigation was to analyze the axial skeleton in fetuses with trisomy 21 and to identify the fields in the axial skeleton affected in this chromosomal disorder.

In earlier studies of the phenotypic characteristics of trisomy 21, interest has chiefly centered on the short limbs with broad hands and short fingers (particularly the fifth finger), depressed nasal bridge, brachycephalic shape of the cranium, tooth agenesis, congenital heart defects, and mental retardation of varying degrees of severity [Penrose and Smith, 1966; Kisling, 1966; Frostad et al., 1971; Opitz et al., 1979; Gilbert and Opitz, 1982; Cuckle et al., 1989; FitzSimmons et al., 1989; Benacerraf et al., 1990, 1991; Johnson et al., 1993a, b, 1994; Keeling, 1993; Nyberg et al., 1993; Russell and Kjær, 1995]. There are also reports on newborn infants with excess skin at the nape of the neck and hypotonia [Benacerraf and Frigoletto, 1987].

Among studies dealing specifically with the fetal skeleton, those on the length and proportions of the bones in the appendicular skeleton constitute the great majority [Cuckle et al., 1989; FitzSimmons et al., 1989; Benacerraf et al., 1991; Rodis et al., 1991; Rotmensch et al., 1992; Johnson et al., 1993a, 1994; Nyberg et al., 1993].

No studies seem to have been published on the axial skeleton in human trisomy 21 fetuses.

MATERIALS AND METHODS

Material

Thirty-one human fetuses (14 males and 17 females) with trisomy 21, gestational ages (GA) 12–24 weeks, were included in the study. Deficient neural tube closure was not present in any fetus.

Contract grant sponsor: Danish Medical Research Council; Contract grant number: 9401187.

*Correspondence to: Inger Kjær, Department of Orthodontics, School of Dentistry, Faculty of Health Sciences, University of Copenhagen, 20 Nørre Allé, DK-2200 Copenhagen N, Denmark.

Received 21 March 1996; Accepted 22 May 1996

The fetuses were examined with parental consent at the Royal Hospital for Sick Children, Edinburgh, Scotland, and at the Hvidovre University Hospital, Copenhagen, Denmark.

Methods

Whole body radiographs in frontal and lateral projections were taken, followed by dissection and further radiologic analysis. A midsagittal tissue block of the cranial base and the entire spine was isolated by two sagittal incisions at the lateral border of the foramen magnum, continuing along the lateral aspects of the entire spine [Kjær, 1990a, 1990b; Kjær et al., 1994a, 1994b]. Radiographs of the interposed midsagittal segment were taken in frontal and lateral projections.

Radiographs of fetal hands and feet were used for skeletal maturity assessment [Kjær, 1974]. Using this standard measurement, standards for the timing and sequence in normal axial skeletal development were calculated and used as a basis for comparison in individual cases [Kjær, 1990a; Kjær et al., 1993; Kyrkanides et al., 1993; Sandikcioglu et al., 1994]. A Grenz Ray radiographic apparatus (Hewlett Packard Faxitron Series 43805N) was used with Kodak X-Omat MA film. The tissue was placed directly on the film envelope. Depending on the size of the specimen, the tube voltage varied between 20 and 60 kV, and the exposure time varied between 10 and 60 seconds at 2.8 to 3.0 mA.

The following seven osseous regions or fields of the axial skeleton illustrated in Figure 1 were analyzed separately: the sacral, lumbar, thoracic, and cervical vertebral segments of the spine; the basilar part of the occipital bone; the postsphenoid component of the sphenoid bone; and the nasal bones.

RESULTS

The axial skeletons of 4 of 31 fetuses were normal (Figs. 2 and 3). The malformations present were composed of the following.

Cranial Base

Basilar part of the occipital bone. There was a unilateral notching of the bone component in 1 of 31

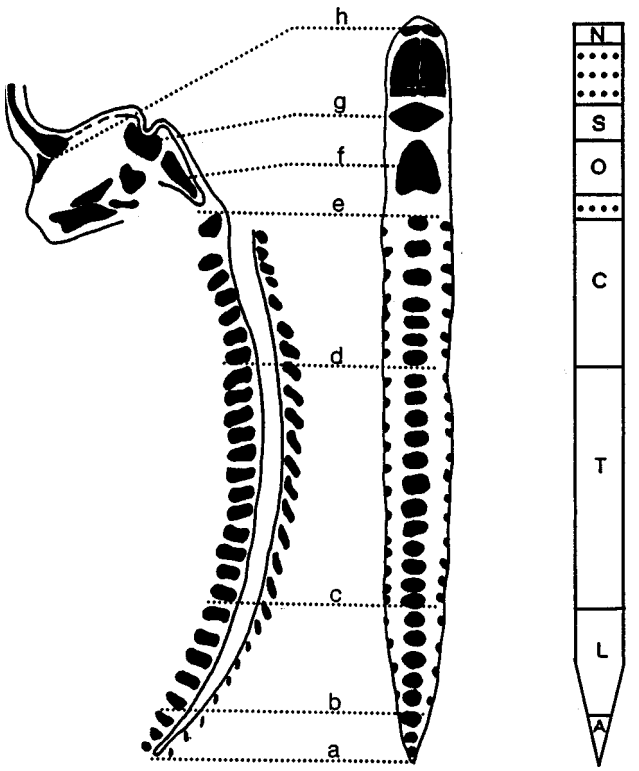

Fig. 1. Drawing of the axial skeleton from a human fetus, 16 w GA, in lateral view (left) and frontal view (right). The lines a–h indicate the axial developmental fields, marked schematically in the frontal view (right). The coccygeal field between the lines a and b is marked A, the lumbar field between the lines b and c is marked L, the thoracic field between the lines c and d is marked T, and the cervical field between the lines d and e is marked C. The basilar part of the occipital bone, indicated by f, is marked O; the postsphenoid bone, indicated by g, is marked S; and the nasal bones, indicated by H, are marked N.

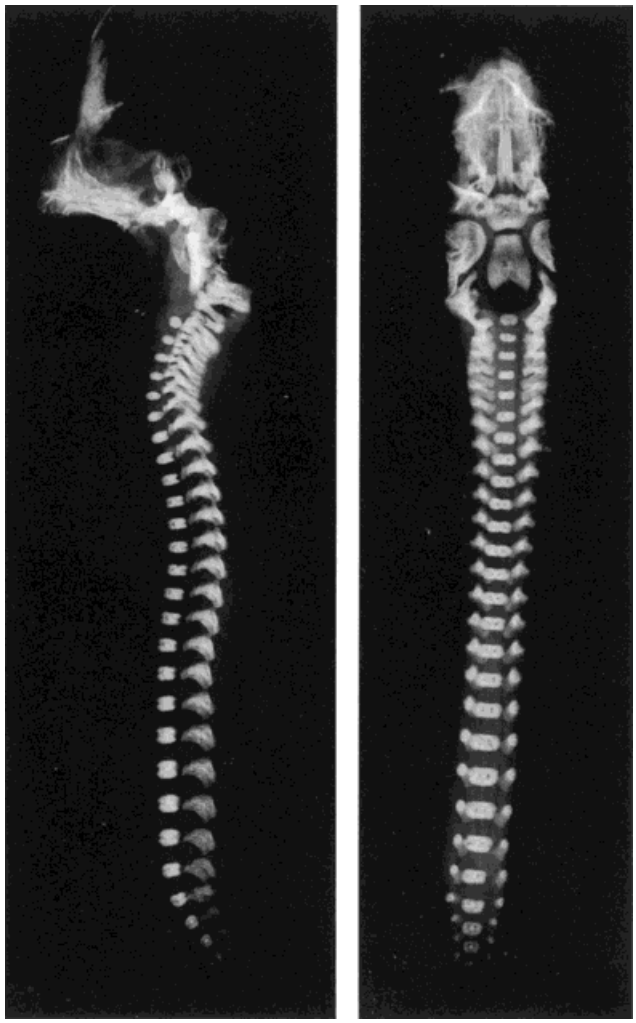

Fig. 2. Radiographs of the axial skeleton of a human fetus with trisomy 21, 20 w GA. **Left:** Lateral view. **Right:** Frontal view. × 0.9. Normal morphology of the axial skeleton.

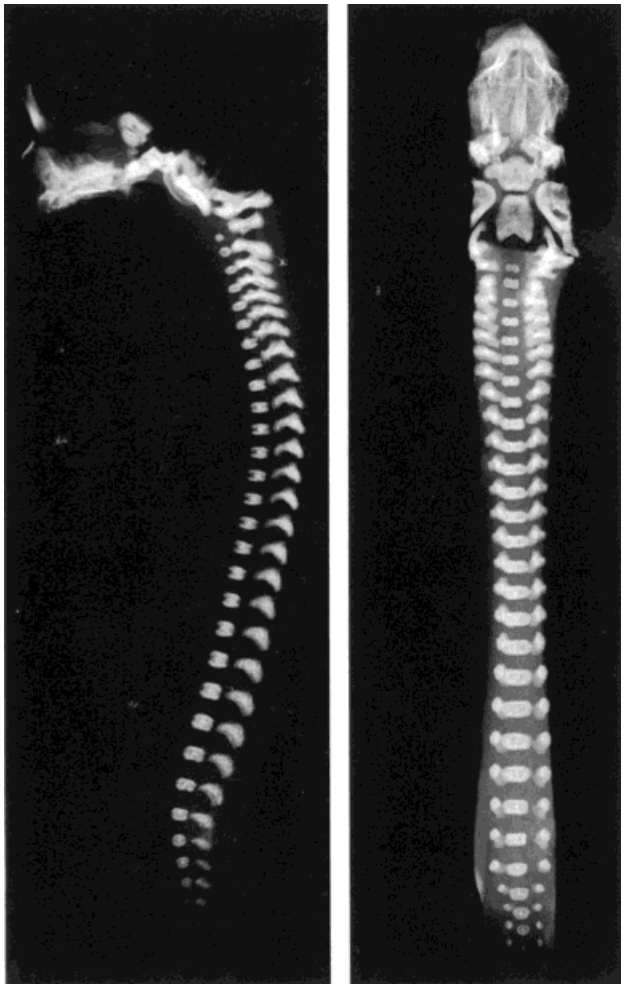

Fig. 3. Radiographs of the axial skeleton of a human fetus with trisomy 21, 21 w GA. **Left:** Lateral view. **Right:** Frontal view. × 0.9. Normal morphology of the axial skeleton.

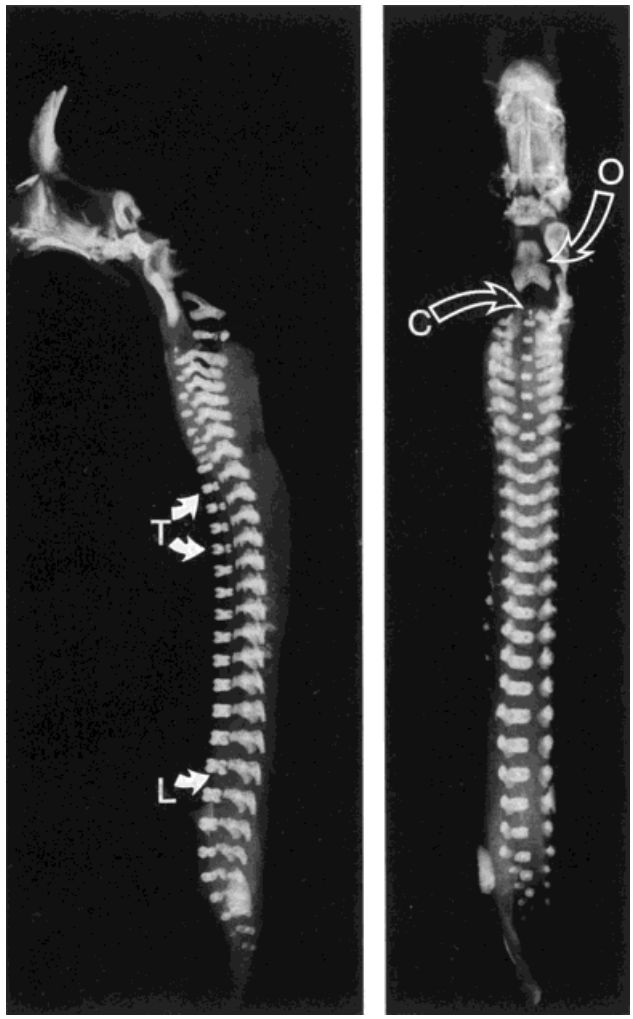

Fig. 4. Radiographs of the axial skeleton of a human fetus with trisomy 21, 20 w GA. **Left:** Lateral view. **Right:** Frontal view. × 0.9. Note unilateral notching of the basilar part of the occipital bone (O), malformation of the upper cervical vertebral body (C), of the thoracic vertebral bodies (T), and of lumbar vertebral body (L).

specimens (Fig. 4). Normal morphology of the basilar part of the occipital bone was seen in the others.

Postsphenoid component of the sphenoid bone. Morphologically, this bone was scallop shaped in all but two fetuses, in which a butterfly shape and a centrally located canal occurred (Fig. 5).

Nasal Bones

Agenesis of nasal bones occurred in 8 of 31 fetuses (Fig. 6). Malformations, such as short nasal bones, occurred in 11 of 31 fetuses (Fig. 5).

Spine

Malformation occurred most frequently in the cervical part of the vertebral column. This was the case in 14 of 31 fetuses (Figs. 4–9). The types of malformations seen were double vertebral bodies, extremely small vertebral bodies, or fused bodies. In some spines, one or more vertebral bodies were absent. Malformations were seen in the thoracic region in 4 of 31 fetuses, and malformations were seen in the lumbosacral region in 8 of 31 fetuses. These malformations were cleft vertebral bodies seen in the lateral view, and butterfly-shaped bodies seen in the frontal view. In one fetus, there was extensive fusion of several vertebral bodies (Fig. 9).

DISCUSSION

The present study describes malformations in the axial skeleton occurring with varying degrees of frequency in the various segments. The most frequent are malformation and agenesis of the nasal bones. Agenesis of the nasal bones was reported previously as occurring postnatally with a frequency of 8% [Frostad et al., 1971]. In the present study, eight fetuses (26%) had nasal bone agenesis. This, together with the hypoplastic nasal bones observed in eleven fetuses, might indicate that some nasal bones in trisomy 21 fetuses develop after the 24th week GA. This does not correspond

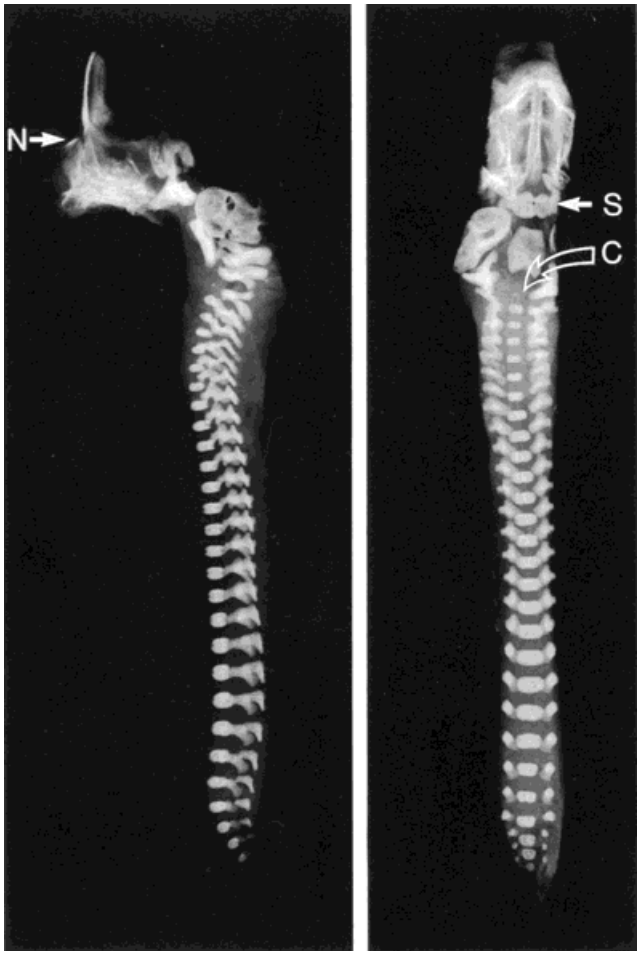

Fig. 5. Radiographs of the axial skeleton of a human fetus with trisomy 21, 21 w GA. **Left:** Lateral view. **Right:** Frontal view. × 0.9. The postsphenoid component of the sphenoid bone (S) appears butterfly shaped with a centrally located canal. The upper cervical vertebral body (C) appears too small for the general osseous stage of development. The nasal bones appear short (N).

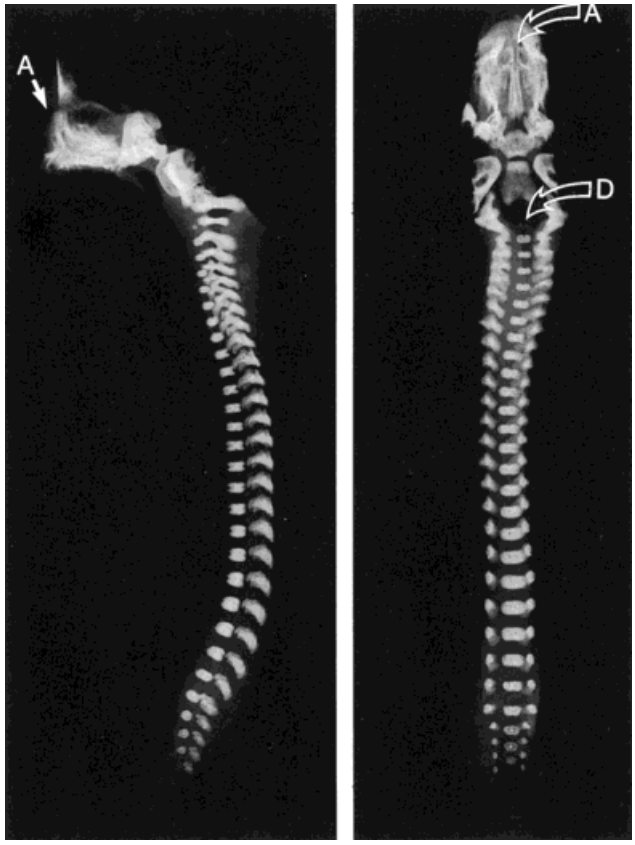

Fig. 6. Radiographs of the axial skeleton of a human fetus with trisomy 21, 21 w GA. **Left:** Lateral view. **Right:** Frontal view. × 0.9. Note agenesis of the nasal bones in the region marked A. The upper cervical vertebral body is malformed. It appears with double vertebral corpora (D).

to the normal age of developmental onset, which is the 10th week GA. The observation of nasal bone agenesis and malformations must be presumed to be related to the flat and narrow bridge of the nose, which is reported as a phenotypic characteristic prenatally and postnatally [Kisling, 1966; Frostad et al., 1971; Keeling, 1993].

The study has also shown that the spinal region most often affected by malformations is the cervical segment. In this connection, it is interesting to observe that a soft tissue nuchal fold has been reported in second trimester fetuses [Benacerraf and Frigoletto, 1987] and that often the neck is short [Keeling, 1993].

In a recently completed study of trisomy 18, malformations were found in other regions of the spine [Kjær et al., 1996]. When the two studies are compared, the two most pronounced differences are (1) that malformations of the basilar part of the occipital bone were present in all cases of trisomy 18 examined, whereas this was almost never seen in trisomy 21, and (2) that

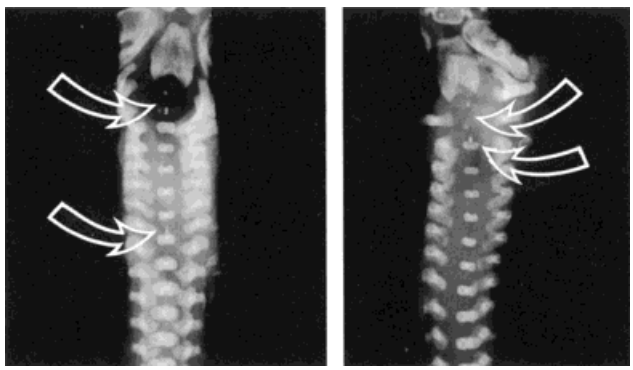

Fig. 7. Radiographs in the frontal view of the cervical part of the axial skeleton from two human fetuses with trisomy 21. Both 18 w GA. × 0.9. **Left:** Extremely small upper cervical vertebral bodies (upper arrow). The first thoracic vertebral body (lower arrow) is malformed. **Right:** Extremely small upper cervical vertebral bodies (upper arrow). The third cervical vertebral body is malformed (lower arrow).

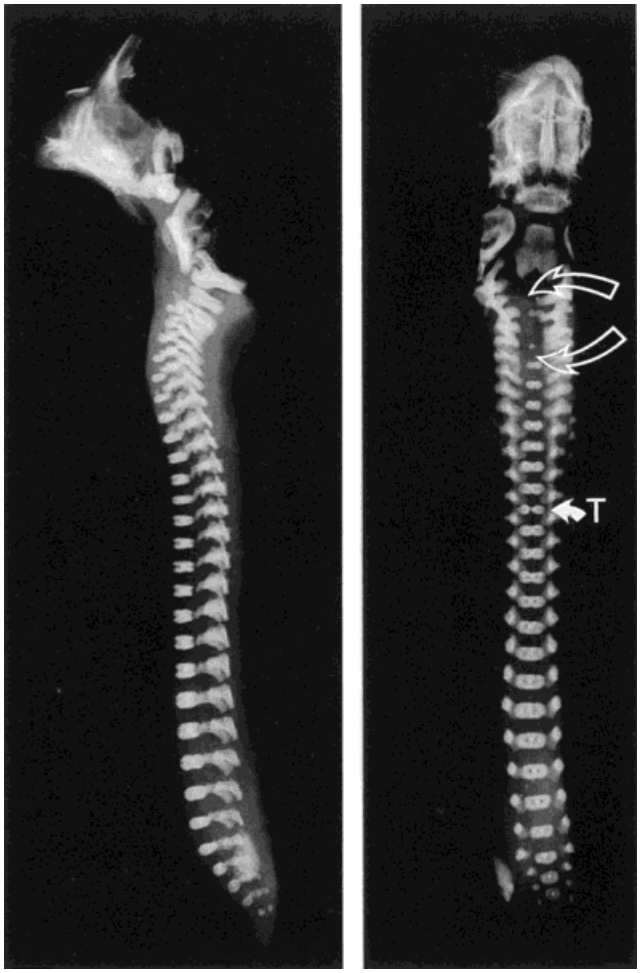

Fig. 8. Radiographs of the axial skeleton of a human fetus with trisomy 21, 20 w GA. **Left:** Lateral view. **Right:** Frontal view. ×0.9. Note malformations of cervical vertebral bodies C1 and C4 as well as the absence of C3 (the region between the arrows). The thoracic vertebral body, T5, appears malformed with double bodies (T).

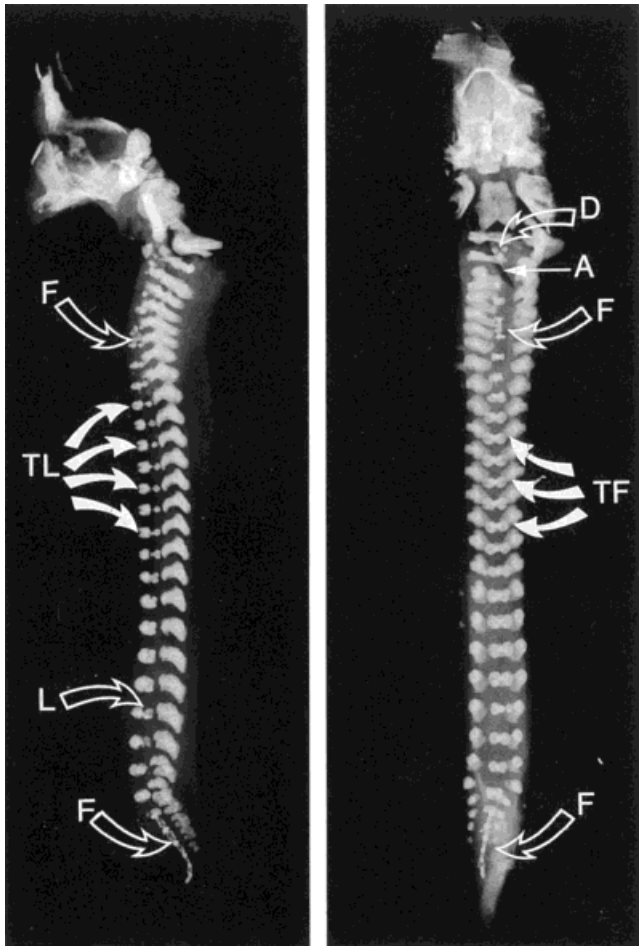

Fig. 9. Radiographs of the axial skeleton of a human fetus with trisomy 21, 20 w GA. **Left:** Lateral view. **Right:** Frontal view. ×0.9. Note extensive fusion of several vertebral bodies in the cervical region and in the coccygeal region, marked by F. The upper cervical vertebral body is malformed. It appears with double vertebral corpora (D). Butterfly-shaped thoracic vertebral bodies are seen in the frontal view (TF). These bodies appear as cleaved bodies in the lateral view (TL). Malformation of bodies is also seen in the lumbar region (L). There is an absence of vertebral body in the region marked A.

the cervical segment was frequently malformed in trisomy 21, whereas this was not observed in the trisomy 18 fetuses.

Two fetuses of the 31 studied differed significantly from the rest. One of them exhibited notching in the basilar part of the occipital bone. The morphology of this notching did not correspond to the notching described in the same bone in trisomy 18 [Kjær et al., 1996]. The fetus in question had the changes in the cervical part of the spine, which we think are characteristic of trisomy 21. In this context, it is interesting to recall the work by Müller and O'Rahilly [1994] on occipitocervical segmentation in human embryos. This work showed that the occipital region consists of several sclerotomes, and one can imagine that different sclerotomes are affected in different genotypes. The second fetus, whose axial skeleton differed from that of the rest, is the one in which fusion of several vertebral bodies—both in the cervical and in the coccygeal region—was registered. Such fused corpora, which may also suggest a notochordal dysfunction, have not been recorded previously in trisomy 21 or in other trisomies [Bersu and Ramirez-Castro, 1977; Colacino and Pettersen, 1978; Ramirez-Castro and Bersu, 1978]. The significance of such a finding is not known. Differences in karyotype in trisomy 21 [Mikkelsen, 1969, 1985] might explain the difference in morphologic appearance in the axial skeleton.

It seems relevant to include the described method of analysis of the axial skeleton in autopsy examination of fetuses. The value of skeletal investigations in autolyzed material has been demonstrated [Kjær and Fischer Hansen, 1995]. In such cases, where chromosome culture is impossible, it is possible that one may speculate about genotype based on examination of the axial skeleton.

Against the background of the data presented here, the results from axial skeletal analysis in trisomy 18

[Kjær et al., 1996], and axial skeletal analysis in different malformations [Kjær, 1994], we recommend that such examinations should form part of future analyses of spontaneous abortions and of fetuses with malformations.

ACKNOWLEDGMENTS

This study was supported by grant no. 9401187 from the Danish Medical Research Council.

REFERENCES

Benacerraf BR, Frigoletto FD (1987): Soft tissue nuchal fold in the second trimester fetus: Standards for normal measurements compared with those in Down's syndrome. Am J Obstet Gynecol 157: 1146–1149.

Benacerraf BR, Harlow BL, Frigoletto FD (1990): Hypoplasia of the middle phalanx of the fifth digit: A feature of the second trimester fetus with Down's syndrome. J Ultrasound Med 9:389–394.

Benacerraf BR, Neuberg D, Frigoletto FD (1991): Humeral shortening in second trimester fetuses with Down syndrome. Obstet Gynecol 77:223–227.

Bersu ET, Ramirez-Castro JL (1977): Anatomical analysis of the developmental effects of aneuploidy in man—the 18-trisomy syndrome: I. Anomalies of the head and neck. Am J Med Genet 1: 173–193.

Colacino SC, Pettersen JC (1978): Analysis of the gross anatomical variations found in four cases of trisomy 13. Am J Med Genet 2: 31–50.

Cuckle H, Wald N, Quinn J, Royston P, Butler L (1989): Ultrasound fetal femur length measurement in the screening for Down's syndrome. Br J Obstet Gynaecol 96:1373–1378.

FitzSimmons J, Droste S, Shepart TH, Pascoe-Mason J, Chinn A, Mack LA (1989): Long-bone growth in fetuses with Down syndrome. Am J Obstet Gynecol 161:1174–1177.

Frostad WA, Cleall JF, Melosky LC (1971): Craniofacial complex in the trisomy 21 syndrome (Down's syndrome). Arch Oral Biol 16: 707–722.

Gilbert EF, Opitz JM (1982): Developmental and other pathologic changes in syndromes caused by chromosome abnormalities. Persp Pediatr Pathol 7:1–63.

Johnson MP, Barr M Jr, Treadwell MC, Michaelson J, Isada NB, Pryde PG, Dombrowski MD, Cotton DB, Evans MI (1993a): Fetal leg and femur: Foot length ratio: A marker for trisomy 21. Am J Obstet Gynecol 169:557–563.

Johnson MP, Michealson JE, Ayoub R, Barr M Jr, Treadwell MC, Isada NB, Reichler A, Hume RF, Evans MI (1993b): Brachycephaly alters biparietal diameter (BPD) in trisomy 21 (T21): Fetal foot length is a better gestational age measurement in sonographic morphologic screening. Am J Hum Genet 53(3):A1423.

Johnson MP, Michaelson JE, Barr M Jr, Treadwell MC, Isada NB, Dombrowski MP, Pryde PG, Addis J, Evans MI (1994): Sonographic screening for trisomy 21: Fetal humerus: Foot length ratio, a useful new marker. Fetal Diagn Ther 9:130–138.

Keeling JW (ed) (1993): "Fetal and Neonatal Pathology," 2nd ed. London: Springer-Verlag.

Kisling E (1966): Cranial morphology in Down's syndrome. Thesis. Royal Danish Dental College, Copenhagen.

Kjær I (1974): Skeletal maturation of the human fetus assessed radiographically on the basis of ossification sequences in the hand and foot. Am J Phys Anthropol 40:257–276.

Kjær I (1990a): Ossification of the human fetal basicranium. J Craniofac Genet Dev Biol 10:29–38.

Kjær I (1990b): Prenatal human cranial development evaluated on coronal plane radiographs. J Craniofac Genet Dev Biol 10:339–351.

Kjær I (1994): The prenatal axial skeleton as marker of normal and pathological development of the human central nervous system. In Lou HC, Greisen G, Larsen JF (eds): "Brain Lesions of the Newborn." Alfred Benzon Symposium 37. Copenhagen: Munksgaard, pp 124–132.

Kjær I, Fischer Hansen B (1995): Postmortem axial skeletal radiography can reveal fetal CNS malformations. APMIS 103:574–581.

Kjær I, Kjær TW, Græm N (1993): Ossification sequence of occipital bone and vertebrae in human fetuses. J Craniofac Genet Dev Biol 13:83–88.

Kjær I, Keeling JW, Græm N (1994a): Cranial base and vertebral column in human anencephalic fetuses. J Craniofac Genet Dev Biol 14:235–244.

Kjær I, Keeling J, Græm N (1994b): Midline maxillofacial skeleton in human anencephalic fetuses. Cleft Palate Craniofac J 31:250–256.

Kjær I, Keeling J, Fischer Hansen B (1996): Pattern of malformations in the axial skeleton in human trisomy 18 fetuses. Am J Med Genet 65:332–336.

Kyrkanides S, Kjær I, Fischer Hansen B (1993): Development of the basilar part of the occipital bone in normal human fetuses. J Craniofac Genet Dev Biol 13:184–192.

Mikkelsen M (1969): Cytogenetiske og autoradiografiske undersøgelser ved Downs syndrom. Thesis. University of Copenhagen.

Mikkelsen M (1985): Down anomaly: New research aspects of an old and well known syndrome. In "Medical Genetics: Past, Present and Future." New York: Alan R. Liss, pp 293–307.

Müller F, O'Rahilly R (1994): Occipitocervical segmentation in staged human embryos. J Anat 185:251–258.

Nyberg DA, Resta RG, Luthy DA, Hickok DE, Williams MA (1993): Humerus and femur length shortening in the detection of Down's syndrome. Am J Obstet Gynecol 168:534–538.

Opitz JM, Herrmann J, Pettersen JC, Bersu ET, Colacino SC (1979): Terminological, diagnostic, nosological, and anatomical-developmental aspects of developmental defects in man. In Harris H, Hirschhorn K (eds): "Advances in Human Genetics." New York: Plenum Press, pp 71–164.

Penrose LS, Smith GF (1966): "Down's Anomaly." London: Churchill Ltd.

Ramirez-Castro JL, Bersu ET (1978): Anatomical analysis of the developmental effects of aneuploidy in man—the 18-trisomy syndrome: II. Anomalies of the upper and lower limbs. Am J Med Genet 2:285–306.

Rodis JF, Vintizelos AM, Fleming AD, Ciarleglio L, Nardi A, Feeney L, Scorza WE, Campbell WA, Ingardia C (1991): Comparison of humerus length with femur length in fetuses with Down syndrome. Am J Obstet Gynecol 165:1051–1056.

Rotmensch S, Luo JS, Liberati M, Belanger K, Mahonny MJ, Hobbins JC (1992): Fetal humeral length to detect Down syndrome. Am J Obstet Gynecol 166:1330–1334.

Russell BG, Kjær I (1995): Tooth agenesis in Down's syndrome. Am J Med Genet 55:466–471.

Sandikcioglu M, Mølsted K, Kjær I (1994): The prenatal development of the human nasal and vomeral bones. J Craniofac Genet Dev Biol 14:124–134.